AMENDMENT

In the claims

Claims 1-39 and 58-73 are pending in this application. Claims 40-47 are withdrawn from consideration based on the Response to Restriction Requirement, filed January 12, 2006, please cancel these claims without prejudice to their future prosecution. Claims 12-16, 18, 21, 23-26, 58, and 65 are amended as follows.

1. – 11. (Cancelled)

12. (Currently amended) A method of determining sequence variations in a target nucleic acid molecule, comprising:

a) cleaving the target nucleic acid molecule into fragments by contacting the target nucleic acid molecule with one or more specific cleavage reagents;

b) cleaving or simulating cleavage of a reference nucleic acid molecule into fragments using the same cleavage reagent(s);

c) determining mass signals of the fragments produced in a) and b);

d) determining differences in the mass signals between the fragments produced in a) and the fragments produced in b);

~~The method of claim 11, wherein determining a set of reduced sequence variation candidates comprises:~~

e~~a~~) identifying fragments that are different between the target nucleic acid and the reference nucleic acid;

f~~b~~) determining compomers corresponding to the identified different fragments in step a) that are compomer witnesses; and

ge) determining a reduced set of sequence variations corresponding to the compomer witnesses that are candidate sequences to determine the sequence variations in the target nucleic acid compared to the reference nucleic acid.

13. (Currently amended) The method of ~~claim 11 or~~ claim 12, wherein the differences in output signals are manifested as missing signals, additional signals, signals that are different in intensity, and/or as having a different signal-to-noise ratio.

14. (Currently amended) The method of ~~claim 11 or~~ claim 12, wherein the masses are determined by mass spectrometry.

15. (Currently amended) The method of any of claims ~~11~~12-14, wherein the sequence variation is a mutation or a polymorphism.

16. (Currently amended) The method of any of claims ~~11~~12-14, wherein the mutation is an insertion, a deletion or a substitution.

17. (Original) The method of claim 15, wherein the polymorphism is a single nucleotide polymorphism.

18. (Currently amended) The method of any of claims ~~1~~12-17, wherein the target is a target nucleic acid molecule from an organism selected from the group consisting of eukaryotes, prokaryotes and viruses.

19. (Original) The method of claim 18, wherein the organism is a bacterium.

20. (Original) The method of claim 19, wherein the bacterium is selected from the group consisting of *Helicobacter pyloris, Borelia burgdorferi, Legionella pneumophilia, Mycobacteria sp. (e.g. M. tuberculosis, M. avium, M. intracellulare, M. kansaii, M. gordonae), Staphylococcus aureus, Neisseria gonorrheae, Neisseria meningitidis, Listeria monocytogenes, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus sp., Streptococcus faecalis, Streptococcus bovis, Streptococcus pneumoniae, Campylobacter sp., Enterococcus sp., Haemophilus influenzae, Bacillus antracis, Corynebacterium diphtheriae, Corynebacterium sp., Erysipelothrix rhusiopathiae, Clostridium perfringens, Clostridium tetani, Enterobacter aerogenes, Klebsiella pneumoniae, Pasturella multocida, Bacteroides sp., Fusobacterium nucleatum, Streptobacillus moniliformis, Treponema pallidium, Treponema pertenue, Leptospira* and *Actinomyces israelli.*

21. (Currently amended) The method of any of claims ~~1~~12-20, wherein a specific cleavage reagent is an RNAse.

22. (Original) The method of claim 21, wherein a specific cleavage reagents are selected from among the RNase T_1, RNase U_2, the RNase PhyM, RNase A, chicken liver RNase (RNase CL3) and cusavitin.

23. (Currently amended) The method of any of claims ~~1~~12-20, wherein a specific cleavage reagent is a glycosylase.

24. (Currently amended) The method of any of claims ~~1~~12-23, wherein sequence variations in the target biomolecule permit genotyping a subject, forensic analysis, disease diagnosis or disease prognosis.

25. (Currently amended) The method of any of claims ~~claim 1~~12-23, wherein the method determines epigenetic changes in a target nucleic acid molecule relative to a reference nucleic acid molecule.

26. (Currently amended) The method of any of claims ~~1~~12-17 that is a method for determining allelic frequency in a sample, comprising:

a) cleaving a mixture of target nucleic acid molecules in the sample containing a mixture of wild-type and mutant alleles into fragments using one or more specific cleavage reagents;

b) cleaving a nucleic acid molecule containing a wild-type allele into fragments using the same cleavage reagent(s);

c) determining mass signals of the fragments;

d) identifying fragments that are different between the mixture of target nucleic acid molecules and the wild-type nucleic acid molecule;

e) determining compomers corresponding to the identified different fragments in step d) that are compomer witnesses;

f) determining allelic variants that are candidate alleles corresponding to each compomer witness;

g) scoring the candidate alleles; and

h) determining the allelic frequency of the mutant alleles in the sample.

27. (Original) The method of claim 26, wherein the allelic frequency is about 5-10%

28. (Original) The method of claim 26, wherein the allelic frequency is less than 5%

29. (Original) A method for determining sequence variations at one or more base positions in a plurality of target nucleic acid molecules, comprising:

a) cleaving the target nucleic acid molecules into fragments by contacting the molecules with one or more specific cleavage reagents;

b) cleaving or simulating cleavage of one or more reference nucleic acid molecules into fragments using the same cleavage reagents;

c) determining the mass signals of fragments produced a) and b);

d) identifying fragments that are different between the target nucleic acid molecules and the one or more reference nucleic acid molecules;

e) determining compomers corresponding to the different fragments that are compomer witnesses;

f) determining the sequence variations that are candidate sequences corresponding to each compomer witness;

g) scoring the candidate sequences; and

h) determining the sequence variations in the plurality of target nucleic acid molecules.

30. (Original) The method of claim 29, wherein after cleaving the target nucleic molecules and the one or more reference molecules into fragments, the fragments are immobilized on a solid support.

31. (Original) The method of claim 30, wherein the fragments comprise an array.

32. (Original) The method of any of claims 29-31, wherein specific cleavage reagents are selected from among RNase T_1, RNase U_2, RNase PhyM, RNase A, chicken liver RNase (RNase CL3) and cusavitin.

33. (Original) The method of any of claims 29-31, wherein specific cleavage reagent is a glycosylase.

34. (Original) The method of claim 30, wherein the array is a chip for mass spectrometry.

35. (Original) A method for detecting sequence variations in a target nucleic acid in a mixture of nucleic acids in a sample, comprising:

a) performing more than one specific cleavage reaction using the same or different specific cleavage reagents on the sample, wherein the target nucleic acid is cleaved in a plurality of fragmentation reactions to generate a plurality of fragmentation patterns;

b) performing or simulating more than one specific cleavage reaction on a reference nucleic acid under conditions that are the same as those of the target cleavage reactions in step a);

c) determining the fragments that are different between the plurality of fragmentation patterns of the cleaved target nucleic acid and the plurality of fragmentation patterns of the cleaved reference nucleic acid;

d) determining the different fragments that are consistent with a particular sequence variation in the target nucleic acid;

e) combining the consistent different fragments corresponding to one or more sequence variations to obtain a spectrum of different fragments;

f) determining, from the spectrum of different fragments, those different fragments containing compomers that are compomer witnesses;

g) determining the sequence variations that are candidate sequences corresponding to each compomer witness;

h) scoring the candidate sequences; and

i) determining the sequence variations in the target nucleic acid molecule in a mixture of nucleic acids in a biological sample.

36. (Original) The method of claim 35, wherein the biological sample is a tumor sample.

37. (Original) The method of claim 35, wherein the biological sample comprises genomic DNA from a pool of individuals.

38. (Original) The method of claims 36 or 37, wherein about 5-10% of the mixture of target nucleic acids contains the sequence variations.

39. (Original) The method of claims 36 or 37, wherein less than 5% of the mixture of target nucleic acids contains the sequence variations.

40. - 57. Cancelled.

58. (Currently amended) The method of claim ~~11~~12, wherein prior to cleaving the target nucleic acid molecule into fragments, the nucleic acid is treated so that the cleavage specificity is altered.

59. (Original) A method for determining single nucleotide polymorphisms at one or more base positions in a plurality of target nucleic acid molecules, comprising:

a) cleaving the target nucleic acid molecules into fragments by contacting the molecules with one or more base specific cleavage reagents;

b) cleaving or simulating cleavage of one or more reference nucleic acid molecules into fragments using the same cleavage reagents;

c) determining the mass signals of fragments produced in a) and b);

d) identifying fragments that are different between the target nucleic acid molecules and the one or more reference nucleic acid molecules;

e) determining compomers corresponding to the identified different fragments in step d) that are compomer witnesses;

f) determining single nucleotide polymorphisms in candidate sequences corresponding to each compomer witness;

g) scoring the candidate sequences; and

h) determining the single nucleotide polymorphisms in the plurality of target nucleic acid molecules.

60. (Original) The method of claim 59, wherein the specific cleavage reagent is an RNase.

61. (Original) The method of claim 59, wherein the specific cleavage reagents are selected from among the RNase T_1, RNase U_2, the RNase PhyM, RNase A, chicken liver RNase (RNase CL3) and cusavitin.

62. (Original) The method of claim 59, wherein the target nucleic acids molecules are selected from among single stranded DNA, double stranded DNA, cDNA, single stranded RNA, double stranded RNA, DNA/RNA hybrid, PNA (peptide nucleic acid) and a DNA/RNA mosaic nucleic acids.

63. (Original) The method of claim 59, wherein the target nucleic acids are produced by transcription.

64. (Original) The method of claim 59, wherein the target nucleic acids comprise genomic DNA from a pool of individuals.

65. (Currently amended) A method of determining single nucleotide polymorphisms in a target nucleic acid molecule, comprising:

a) cleaving the target nucleic acid molecule into fragments by contacting the target nucleic acid molecule with one or more base specific cleavage reagents;

b) cleaving or simulating cleavage of a reference nucleic acid molecule into fragments using the same cleavage reagent(s);

c) determining mass signals of the fragments produced in a) and b);

d) determining differences in the mass signals between the fragments produced in a) and the fragments produced in b); ~~and~~

f) determining compomers corresponding to the identified different fragments in step b) that are compomer witnesses; and

g) determining a reduced set of single nucleotide polymorphism candidates corresponding to the compomer witnesses that are candidate sequences to determine the single nucleotide polymorphisms in the target nucleic acid compared to the reference nucleic acid.

~~e) determining a reduced set of single nucleotide polymorphism candidates from the differences in the mass signals and thereby determining single nucleotide polymorphisms in the target compared to the reference nucleic acid.~~

66. (Original) The method of claim 65, wherein the specific cleavage reagent is an RNase.

67. (Original) The method of claim 65, wherein a specific cleavage reagents are selected from among the RNase T_1, RNase U_2, the RNase PhyM, RNase A, chicken liver RNase (RNase CL3) and cusavitin.

68. (Original) The method of claim 65, wherein the target nucleic acids molecule is selected from among single stranded DNA, double stranded DNA, cDNA, single stranded RNA, double stranded RNA, DNA/RNA hybrid, PNA (peptide nucleic acid) and a DNA/RNA mosaic nucleic acid.

69. (Original) The method of claim 65, wherein the target nucleic acid is produced by transcription.

70. (Original) The method of claim 65, wherein the target nucleic acid is genomic DNA from a single individual.

71. (Original) The method of claim 65, futher comprising scoring the reduced set of single nucleotide polymorphism candidates.

72. (Original) The method of claim 65, further comprising scoring heterozygous single nucleotide polymorphism candidates.

73. (Original) The method of claim 65, further comprising scoring homozygous single nucleotide polymorphism candidates.